Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicenter case-control study

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Although numerous reports indicate that patients receiving autotransplants for lymphoma are at increased risk for myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), the separate contributions of pretransplantation- and transplantation-related therapy are not well characterized. We conducted a case-control study of 56 patients with MDS/AML and 168 matched controls within a cohort of 2 739 patients receiving autotransplants for Hodgkin disease or non-Hodgkin lymphoma at 12 institutions (1989-1995). Detailed abstraction of medical records was undertaken to determine all pre- and post-transplantation therapy, and transplantation-related procedures. In multivariate analyses, risks of MDS/AML significantly increased with the intensity of pretransplantation chemotherapy with mechlorethamine (relative risks [RRs] = 2.0 and 4.3 for cumulative doses < 50 mg/m^2 and ≥ 50 mg/m,^{2} respectively; trend over dose categories, *P* = .04) or chlorambucil (RRs = 3.8 and 8.4 for duration < 10 months or ≥ 10 months, respectively; trend, *P* = .009), compared with cyclophosphamide-based therapy. Transplantation-conditioning regimens including total-body irradiation (TBI) at doses 12 Gy or less did not appear to elevate leukemia risk (RR = 1.3; *P* = .48) compared with non-TBI regimens; however, a statistically significant increased risk was found for TBI doses of 13.2 Gy (RR = 4.6; *P* = .03). Peripheral blood stem cells were associated with a nonsignificant increased risk of MDS/AML (RR = 1.8; *P* = .12) compared with bone marrow grafts. Our data show that type and intensity of pretransplantation chemotherapy with alkylating agents are important risk factors of MDS/AML following autotransplantation. Transplantation-related factors may also modulate this risk; however, the apparent contribution of high-dose TBI requires confirmation. (Blood. 2003;101:2015-2023)

Introduction

A large number of reports indicate that lymphoma patients who receive autologous transplantation with high-dose conditioning regimens are at increased risks for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).[1-13] This late complication has important clinical implications since autotransplantations are a successful and increasingly used treatment for patients with recurrent and relapsed lymphoma.[14-17] Studies investigating the relative contribution of pretransplantation and transplantation therapies in the development of MDS/AML report inconsistent findings, in part because of incomplete data on type, duration, and dose of chemotherapy and radiotherapy received before transplantation.[3,6-11,18] Quantification of the risk associated with prior therapy

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is critical in the evaluation of transplantation-related factors, since conventional therapy may include alkylating agents known to induce leukemia (eg, mechlorethamine),[19-22] and other potentially leukemogenic regimens, such as high-dose, extended-field radiotherapy.[23,24] Most studies of MDS/AML following autotransplantation are limited by small numbers of cases,[3,5,7,9,11,13,25] and little variation in transplantation conditioning regimens.[6,8,9,13] We present a case-control study of 56 lymphoma patients with secondary MDS/AML treated in 12 transplantation centers that participate in the Autologous Blood and Marrow Transplant Registry (ABMTR). Our objective is to evaluate leukemia risks associated with pre- and posttransplantation factors and transplantation-related procedures.

Patients and methods

Study patients

Patients developing MDS/AML and matched controls were identified from a cohort of 2 739 patients receiving autotransplants for lymphoma (955 Hodgkin disease [HD] and 1 784 non-Hodgkin lymphoma [NHL]) at 12 ABMTR centers. Centers were selected for participation based on completeness of follow-up for transplant recipients, identification of at least one patient with MDS/AML, and willingness to collect detailed pretransplantation treatment data. Patient eligibility criteria included treatment with one or more autotransplantations for lymphoma between 1989 and 1995 with follow-up through December 31, 1996, (mean, 28 months; median, 21 months; range, < 1 month-8 years), and no allogeneic transplantation or invasive primary cancer other than HD or NHL prior to diagnosis of MDS/AML or corresponding follow-up date for controls.

There were 57 patients reported as developing MDS/AML. Independent review of all available pathology reports and bone marrow specimens (n = 55 including 46 with centralized review [CYL] and 9 with expert review at the institution), and/or cytogenetic reports (n = 37) confirmed the diagnosis in 56; some of them were reported previously.[1-3,5,11] Statistical analyses with and without 2 MDS cases for which a re-review of bone marrow slides was not possible led to similar results.

For each subject with confirmed MDS/AML, 3 matched controls were randomly selected from the entire cohort. Matching criteria were primary disease (HD/NHL), sex, race, age at transplantation (± 5 years), and survival without a secondary neoplasm at least as long as the interval between the date of transplantation and the diagnoses of MDS/AML for the corresponding case.

Treatment and risk factors

Information on transplantation procedures was available from ABMTR files, including source of stem cells (bone marrow [BM], peripheral blood stem cells [PBSCs]); conditioning chemotherapy; total body irradiation (TBI) with doses; mobilization therapy (chemotherapy, growth factors); graft purging; number of autotransplantations; and platelet and granulocyte recovery after transplantation. Because detailed information on lymphoma therapy given before and after transplantation is not routinely collected by the ABMTR, a comprehensive review of medical records was conducted for each case and control to confirm disease status at transplantation, and to determine all pre- and posttransplantation treatments. Data abstraction was undertaken up to the diagnosis date of MDS/AML in cases and the comparable matched interval for controls. Treatment information was collected by trained abstractors using standardized forms and validated by an independent reviewer. Sources of data included medical charts from referring hospitals/clinics, radiotherapy facilities, and transplantation centers. When therapy records were deemed incomplete, attempts were made to contact the primary physician for additional data on the patient's earlier treatment.

We obtained information on chemotherapy protocols, duration of administration of all cytotoxic agents, and cumulative doses for selected drugs, including mechlorethamine, procarbazine, and the DNA topoisomerase II inhibitors (primarily etoposide). Data on radiotherapy fields and doses were collected and classified by a radiation dosimetrist according to estimated level of radiation dose to total active bone marrow (ABM) using previously described methods.[26] Each patient was placed into one of 3 broad categories of radiation exposure (low, medium, high), based on approximate measures of total ABM exposure derived from previous work on radiation dosimetry. Generally, patients classified in the "low" exposure group received radiotherapy limited to a limb, head, neck, or other minor field; "medium" exposure group corresponded to low to moderate irradiation doses to mantle/mediastinal fields (mean, 2 980 cGy) or subdiaphragmatic fields (mean, 3 140 cGy; eg, inverted Y, para-aortic, and pelvic); and "high" exposure included high-dose irradiation to mantle/mediastinal fields (mean, 3 900 cGy) or subdiaphragmatic fields (mean, 4 200 cGy), or sub- or total lymphoid irradiation.

Statistical analysis

Univariate and multivariate analyses were conducted using conditional logistic regression[27,28]; multivariate relative risks (RRs) are presented in the text and tables. The RRs of secondary MDS/AML were estimated for HD and NHL patients combined, and separately for each primary disease. Log-likelihood ratio tests were conducted and 2-sided 95% confidence intervals (CIs) computed. We present the cumulative incidence of secondary MDS/AML, the most appropriate measure to be used in the presence of competing risks.[29] We also computed the cumulative probabilities (Kaplan-Meier),[30] an alternate method often used in previous publications.

In the present study, all but one patient (a case) had received one or more alkylating agents prior to transplantation. We grouped patients into mutually exclusive categories based on total chemotherapy history, utilizing a priori evidence about the leukemogenicity of the administered alkylating agent(s).[19-21,31-35] Because low-dose cyclophosphamide is associated with generally low leukemia risks,[19,20,34] we selected as the reference group those patients who received only cyclophosphamide-based regimens (ie, CHOP, CVP, MACOP-B, PROMACE) without exposure to other alkylating agents (except ifosfamide); about 44% of patients in this group also received etoposide. The remaining patients were categorized in the following treatment groups: (1) MOPP (mechlorethamine, vincristine, procarbazine, prednisone) or MOPP-like regimens (referred to as MOPP), including mechlorethamine and/or procarbazine with or without other alkylating agents; (2) chlorambucil-based regimens with or without other alkylating agents (no MOPP); and (3) other alkylating agents (no MOPP, no chlorambucil), a category which included cisplatin (n = 46), procarbazine (n = 14), carmustine (n = 10), and melphalan (n = 10). Additional analyses considered cumulative dose of mechlorethamine, procarbazine, and the epipodophyllotoxins, and duration of chlorambucil use. Information on dose was available for 75% of patients with mechlorethamine/procarbazine and 83% of those with etoposide. Missing doses were estimated by multiplying the number of months of therapy by the mean monthly dose for the specific drug among controls. For dose-response analyses, patients were categorized into 2 groups based on the median value of cumulative dose (mg/m^2) of selected drugs or total duration (months) for chlorambucil. Tests for trend were conducted using categoric variables.

Results

Secondary MDS/AML occurred in 19 patients who underwent autotransplantation for HD and in 37 who underwent transplantation for NHL. The cumulative incidence rate for developing MDS/AML at 7 years was 3.7% (95% CI, 2.7-4.6) in the entire cohort (N = 2 739). It was 3.9% (95% CI, 2.6-5.2) in the 1 784 patients who underwent transplantation for NHL and 3.3% (95% CI, 1.8-4.7) in the 955 patients who underwent transplantation for HD. The 7-year cumulative probabilities using the Kaplan-Meier method were 8.1% (95% CI, 5.1-11.0) in the entire cohort, 8.9% (95% CI, 4.8-12.9) for patients with NHL, and 7.1% (95% CI, 2.8-11.3) for those with HD. However, it should be noted that, in

contrast to cumulative incidence rates, the Kaplan-Meier approach does not adjust for competing risks, and therefore may overestimate risks in the presence of substantial censoring due to death from causes other than second cancers.

Clinical and morphologic characteristics of MDS/AML cases

Secondary MDS/AML occurred on average 2.5 years after transplantation (median, 2.5 years; range, 3 months-7 years). In the first year afer transplantation, 11 case patients, including 4 within 6 months of transplantation, were diagnosed. By the end of study, 43 of the 56 patients died. Mean survival was 6 months (median, 2 months; range, $<$ 1 month-2 years) after diagnoses of AML and 12 months (median, 8 months; range, $<$ 1 month-6 years) after diagnoses of MDS.

Histologic types of secondary MDS (n = 46) included 1 RA, 9 RAEB, 4 RAEB-T, 1 RARS, and 4 CMML, according to the French-American-British (FAB) criteria[36]; 9 refractory cytopenia with multilineage dysplasia according to the World Health Organization classification system[37]; 6 atypical MDSs with myelofibrosis; and 12 unclassified MDSs (including 8 cases with bone marrow specimens reviewed at the institution). Acute myeloid leukemias (n = 10) included the following FAB subtypes:[38] M1 (n = 1), M2 (n = 3), M4 (n = 2), M5 (n = 1), and M7 (n = 1), and unclassified type (n = 2). Clonal abnormalities were present in 33 of 37 patients with cytogenetic reports, including 25 with deletions of chromosomes 5 and/or 7 and 6 with abnormalities involving chromosomes 1, 6, 8, 10, or 11. Only 2 patients had balanced translocations 11q23, including one who received etoposide therapy before transplantation.

Pretransplantation risk factors

Characteristics of MDS/AML cases and matched controls are presented in Table 1. All but one of the 224 study patients received alkylating based regimens prior to transplantation. MOPP or MOPP-like therapy was given in about one third of cases and controls, mostly for patients with HD. Case patients, especially those with NHL, were more frequently treated with chlorambucil-based regimens than controls (16.1% versus 4.2%). About 48% of both cases and controls received etoposide before transplantation. Slightly less than 50% of all patients received radiotherapy in addition to chemotherapy. A larger proportion of MDS/AML cases than controls had multiple remissions/relapses before undergoing transplantation (Table 1).

The relative risks of MDS/AML associated with specific pretransplantation chemotherapy regimens for NHL and HD patients combined were first computed with no adjustment for transplantation-related factors (Table 2). Compared with the reference group of patients given only cyclophosphamide-based regimens, significantly higher risks of MDS/AML were observed in patients receiving MOPP (RR = 4.8; P = .02), chlorambucil (RR = 10.8; P = .0002), or other alkylating agents, including procarbazine, cisplatin, melphalan, or carmustine (RR = 2.8; P = .02; Model 1, Table 2). Risk rose with increasing cumulative dose of mechlorethamine (RR = 3.1 and 6.6 for doses $<$ 50 mg/m^2 and $\geq$ 50 mg/m,^{2} respectively, P_{trend} = .01; Model 2, Table 2), but not procarbazine (data not shown). Risk also rose with longer durations of chlorambucil therapy (P_{trend} = .0002; RR = 16.5 for duration $\geq$ 10 months; Model 3, Table 2). There was no association between pretransplantation therapy with etoposide and MDS/AML (RR = 0.9; P = .71), even when cumulative doses were considered (RR = 0.64 for doses 0.1-0.87 g/m^2 [median value] based on 12 cases and 42 controls, and RR = 1.14 for doses $\geq$ 0.88 g/m^2 based on 15 cases and 40 controls; P_{trend} = .85). We found no increase in MDS/AML risk for patients exposed to either medium (RR = 1.5; P = .35) or high (RR = 1.1; P = .79) doses of radiation to active bone marrow prior to transplantation, compared with those with no or low-dose exposure (Table 3). A decreased risk of borderline significance was seen with splenectomy (RR = 0.3; 95% CI, 0.06-0.96; P = .04), based on only 3 case patients. There was no association between MDS/AML and disease status at transplantation (RR = 1.1; 95% CI, 0.49-2.41 for $\geq$ 2 relapses or $\geq$ 3 complete remissions [CRs] versus 1 relapse, $\leq$ 2 CR, or no CR; P = .81) or interval between lymphoma diagnosis and transplantation ($<$ 4 years versus $\geq$ 4 years; RR = 1.0; 95% CI, 0.44-2.08; P = .94).

We also evaluated pretransplantation risk factors of MDS/AML separately in NHL and HD. Among NHL patients, the magnitude of the risks associated with chlorambucil (RR = 10.5; 95% CI, 3.0-42.52) or other alkylating agents (RR = 2.9; 95% CI, 1.22-7.32) was similar to that reported for all patients. Histologic type of NHL did not appear to affect MDS/AML risk after adjustment for pretransplantation therapy (RR = 1.2 for low versus intermediate or high grade NHL; P = .74). Separate analysis of HD patients was limited by lack of variation in pretransplantation regimens; 17 of 19 cases and 48 of 57 controls received at least one course of MOPP. However, there was a suggestion for a higher MDS/AML risk with high cumulative doses ($\geq$ 50 mg/m^2) of mechlorethamine (RR = 2.5; P = .10). There was also some indication for an increased risk with pretransplantation radiotherapy for HD, but not NHL, (RR = 2.7; 95% CI, 0.80-12.30; P = .12), although there was no apparent relation with dose. Nonsignificant 2.5- to 3-fold increased risks of MDS/AML were observed following irradiation to the chest and abdominal fields, respectively (data not shown).

Transplantation-related factors

Case patients received more frequently PBSC alone or in combination with BM than a BM graft alone compared with controls (66% versus 46%, Table 1). Most patients with PBSC graft received growth factors to mobilize stem cells and 15% were given mobilization (priming) chemotherapy. Conditioning regimens with TBI were used mainly for NHL patients, with a larger proportion of cases than controls receiving TBI at dose 13.2 Gy (Table 1).

Table 4, Model 1, presents MDS/AML risks associated with transplantation-related factors without adjustment for pretransplantation chemotherapy. We found a statistically significant increase in risk with peripheral blood stem cell (PBSC) versus bone marrow grafts (RR = 2.3; P = .01). Overall, there was a nonsignificant excess risk of MDS/AML with use of conditioning regimens with TBI, compared with no TBI (RR = 2.0; 95% CI, 0.95-4.18; P = .07). The dose-response analysis revealed that the excess risk was limited to patients receiving TBI doses of 13.2 Gy (RR = 6.6; P = .003; Table 4, Model 1), a regimen used at one transplantation center in our series. Those with lower TBI doses (5-12 Gy) had no evidence of elevated risk of MDS/AML. After adjustment for pretransplantation chemotherapy (Table 4, Model 2), the magnitude of the associations observed with transplantation-related factors and MDS/AML risk was slightly lower, and the association with PBSC was no longer statistically significant (RR = 1.8; P = .12). The intensity of pretransplantation therapy with MOPP or chlorambucil remained a significant predictor of MDS/AML in the fully adjusted model (P_{trend} = .04 and .009, respectively; Table 4, Model 2).

Table 1. Characteristics of patients developing secondary myelodysplastic syndrome or acute myeloid leukemia after autotransplantation for lymphoma, and matched controls

Characteristics	Cases, n = 56 (no., %)	Controls, n = 168 (no., %)
Pretransplantation characteristics		
Primary disease		
Hodgkin disease	19 (33.9)	57 (33.9)
Nodular sclerosis	14 (25.0)	38 (22.6)
Mixed cellularity	5 (8.9)	10 (6.0)
Other types[a]	0 (0)	9 (5.4)
Non-Hodgkin lymphoma[b]	37 (66.1)	111 (66.1)
Low grade	17 (30.4)	35 (20.8)
Intermediate grade	7 (12.5)	46 (27.4)
High grade	7 (12.5)	16 (9.5)
Other types[c]	6 (10.7)	14 (8.3)
Male sex	30 (53.6)	90 (53.6)
Splenectomy	3 (5.4)	22 (13.2)
Pretransplantation chemotherapy with alkylating agents		
MOPP/MOPP-like regimen (mechlorethamine/procarbazine-based)	20 (35.7)	55 (32.7)
Other regimens (non-MOPP)	36 (64.3)	113 (67.3)
Cyclophosphamide-based regimen, no other alkylating agents[d]	8 (14.3)	59 (35.1)
Chlorambucil-based regimen ± other alkylating agents[e]	9 (16.1)	7 (4.2)
No chlorambucil, other alkylating agents[f]	18 (32.1)	47 (28.0)
No alkylating agents[g]	1 (1.8)	0 (0)
Pretransplantation chemotherapy with etoposide	27 (48.2)	82 (48.8)
Pretransplantation radiotherapy fields		
No radiotherapy	30 (53.6)	97 (57.7)
Mantle/mediastinum[h]	10 (17.9)	28 (16.7)
Inverted Y and/or other fields below diaphragm[i]	3 (5.4)	17 (10.1)
Total lymphoid irradiation or subtotal lymphoid irradiation[j]	4 (7.1)	14 (8.3)
Other fields[k]	9 (16.1)	12 (7.1)
Disease status at transplantation		
Never in complete remission	12 (21.4)	41 (24.4)
First complete remission	6 (10.7)	19 (11.3)
Second or third complete remission	14 (25.0)	30 (17.9)
First relapse	13 (23.2)	55 (32.7)
2 or more relapses	11 (19.7)	23 (13.7)
Interval between lymphoma diagnosis and transplantation		
Mean/median	3.5 y/2.0 y	3.0 y/2.0 y
Range	3 mo-21 y	3 mo-24 y
Transplantation characteristics		
Age at transplantation, y		
8 to 30	12 (21.4)	36 (21.4)
31 to 40	24 (42.9)	62 (36.9)
41 to 61	20 (35.7)	70 (41.7)
Calendar year of transplantation		
1989-1990	24 (42.9)	47 (28.0)
1991-1993	23 (41.1)	90 (53.6)
1994-1995	9 (16.1)	31 (18.5)
Source of stem cells		
Bone marrow	19 (33.9)	90 (53.6)
Peripheral blood	31 (55.4)	64 (38.1)
Bone marrow and peripheral blood	6 (10.7)	14 (8.3)
Conditioning regimen		
TBI + cyclophosphamide	16 (28.6)	23 (13.7)
TBI + VP-16 ± cyclophosphamide	10 (17.9)	34 (20.2)
VP-16 + cyclophosphamide ± other drugs	21 (37.5)	76 (45.2)
VP-16, no cyclophosphamide ± other drugs	7 (12.5)	21 (12.5)
Others	2 (3.6)	14 (8.3)
TBI dose, Gy		
None	30 (53.6)	111 (66.1)
5.0 or 10.0	4 (7.1)	13 (7.7)
12.0	14 (25.0)	39 (23.2)
13.2	8 (14.3)	5 (3.0)
Purging of harvested stem cells[l]	6 (11.1)	20 (12.7)
Mobilization (priming) chemotherapy[m]	7 (12.5)	14 (8.5)

Table 1. Characteristics of patients developing secondary myelodysplastic syndrome or acute myeloid leukemia after autotransplantation for lymphoma, and matched controls (continued)

Characteristics	Cases, n = 56 (no., %)	Controls, n = 168 (no., %)
Posttransplantation characteristics		
Disease status		
Complete remission	36 (64.3)	124 (73.8)
Persistent or recurrent disease	19 (33.9)	40 (23.8)
Unknown disease status	1 (1.8)	4 (2.4)
Posttransplantation chemotherapy with alkylating agent[n]	6 (10.7)	17 (10.1)
Posttransplantation chemotherapy with etoposide	4 (7.1)	14 (8.3)
Posttransplantation radiotherapy	13 (23.2)	22 (13.1)
Posttransplantation growth factors[m]	41 (73.2)	112 (68.3)

Controls matched to cases on primary disease (NHL, HD), sex, race, age at transplantation (± 5 years) and latency (time between transplantation and MDS for the cases and corresponding interval in controls).

Co indicates control(s); Ca, case patient(s); AA, alkylating agents; CTX, cyclophosphamide; CDDP, cisplatin; IFO, ifosfamide; BCNU, carmustine; LPAM, melphalan; PROC, procarbazine; DTIC, dacarbazine; VCR, vincristine; DNM, daunomycin; MTX, methotrexate; CHLB, chlorambucil; and NITM, nitrogen mustard.

[a]Other histologic types include: lymphocyte predominant (1 Co), lymphocyte depleted (2 Co), and unclassified or ill-defined type (6 Co).

[b]Lymphomas are defined according to the International Working Formulation, National Cancer Institute.

[c]Other histologic types include: composite lymphoma (2 Ca/6 Co); large cell (Ki-1$^+$) lymphoma (1 Ca/1 Co); and unclassified lymphoma (3 Ca/7 Co).

[d]One case and 8 controls received ifosfamide in addition to cyclophosphamide; category includes patients treated with etoposide.

[e]AA in addition to chlorambucil include: CTX (6 Ca/1 Co); CTX + CDDP (1 Ca/1 Co); CDDP (1 Ca); CTX + IFO (2 Co); CTX + BCNU + LPAM (1 Co); PROC (1 Co); PROC + CTX (1 Co).

[f]AA include: CTX + CDDP (7 Ca/23 Co); CTX + PROC (1 Ca/6 Co); CTX + BCNU (1 Ca/3 Co); CTX + IFO + CDDP (4 Ca/4 Co); CTX + CDDP + PROC (1 Ca/4 Co); CTX + BCNU + LPAM + CDDP (1 Ca); CTX + IFO + PROC (2 Co); LPAM + BCNU (2 Ca/2 Co); CDDP (1 Ca); CDDP + IFO + BCNU (1 Co); DTIC (2 Co).

[g]One case received VCR + DNM + MTX.

[h]One control received mantle and pelvic irradiation.

[i]Includes the following fields alone or in combination: inverted-Y, para-aortic field, abdomen, spleen, and pelvis.

[i]Subtotal lymphoid irradiation (STLI) includes mantle field, splenic pedicle, and para-aortic field; total lymphoid irradiation (TLI) includes S-TLI and inverted-Y.

[k]Includes the following fields alone or in combination: head/neck, chest, spine, sacrum, limb, groin, and TBI (low dose).

[l]Data were not available for 2 case patients and 10 controls.

[m]Data were not available for 4 controls.

[n]AA include: CTX (3 Ca/6 Co); CDDP (2 Co); CTX + CDDP (1 Co); IFO + CDDP (1 Ca/2 Co); CHLB (1 Co); PROC + CHLB (1 Ca/1 Co); PROC + CTX (1 Co); NITM + BCNU (1 Co); NITM + BCNU + CTX (1 Co); NITM + PROC (1 Ca/1 Co).

Conditioning TBI. We identified several factors correlated with use of TBI dose 13.2 Gy, which may have influenced leukemia risks reported in these patients. All 8 cases given high-dose (13.2 Gy) TBI were NHL patients who received transplants with PBSC grafts. Among them, 4 received chlorambucil prior to transplantation, which was associated with an elevated risk of MDS/AML in this study. Additionally, 3 cases were diagnosed with MDS within the first 8 months (5, 7, and 8 months) following transplantation, suggesting that pretransplantation therapy played an important role in the development of the preleukemic condition. We further explored the risk associated with TBI by excluding early-onset (≤ 18 months) MDS/AML cases and their matched controls from the analyses; risks for the high-dose TBI group were then somewhat lower and nonsignificant (RR = 3.8; 95% CI, 0.70-21.12). The relative risk for TBI dose 12 Gy or less among the 18-month survivors was 1.7 (95% CI, 0.68-4.53).

Our analysis suggested that increased risk of MDS/AML following conditioning with TBI (versus no TBI) was limited to

Table 2. Risk of myelodysplastic syndrome and acute myeloid leukemia following autologous transplantation for lymphoma according to type and intensity of pretransplantation chemotherapy, without adjustment for transplantation-related factors

Risk factors	Cases/controls	RR	95% CI	*P*
Model 1:* type of pretransplantation chemotherapy				
Cyclophosphamide, no other AA	9/59	1.0	—	—
MOPP regimen ± other AA	20/55	4.8	1.27-18.54	.02
Chlorambucil, no MOPP regimen ± other AA	9/7	10.8	3.06-42.52	.0002
Other AA, no MOPP regimen, no chlorambucil	18/47	2.8	1.20-7.32	.02
Model 2:† cumulative dose of mechlorethamine (MOPP regimen)				
Less than 50 mg/m^2	8/31	3.1	0.76-12.81	.11
50 mg/m^2 or higher	12/24	6.6	1.57-29.37	.01
				P_{trend} .01
Model 3:‡ duration of chlorambucil therapy				
Less than 10 months	4/5	7.1	1.38-38.86	.02
10 months or longer	5/2	16.5	3.06-130.32	.001
				P_{trend} .0002

RR indicates relative risk; CI, confidence interval; AA, alkylating agents; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; and —, reference group.

*RRs are adjusted for pretransplantation radiotherapy (1 variable); subjects in cyclophosphamide group (eg, CHOP, CVP, MACOP-B) did not receive other alkylating agents (except ifosfamide given in 1 case and 8 controls). Subjects in MOPP group may have received other alkylating agents; subjects in chlorambucil group may have received other alkylating agents, except MOPP regimen.

†Reference group consists of patients treated with cyclophosphamide-based regimen only (refer to Model 1). RRs are adjusted for duration of chlorambucil (2 variables) and therapy with other alkylating agents (1 variable).

‡Reference group consists of patients treated with cyclophosphamide-based regimen only (refer to Model 1). RRs are adjusted for cumulative dose of mechlorethamine (2 variables) and therapy with other alkylating agents (1 variable).

Table 3. Risk of myelodysplastic syndrome and acute myeloid leukemia following autologous transplantation for lymphoma according to pretransplantation radiotherapy and radiation dose to active bone marrow, without adjustment for transplantation-related factors

Risk Factors	Cases/controls	RR	95% CI	*P*
Model 1:* pretransplantation radiotherapy				
No	32/102	1.0	—	—
Yes	24/66	1.4	0.68-2.89	.37
Model 2:† radiation dose to active bone marrow				
No	32/102	1.0	—	—
Medium‡	12/29	1.5	0.63-3.71	.35
High§	12/37	1.1	0.46-2.75	.79
				P_{trend} .75

RR indicates relative risk; CI, confidence interval; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; and —, reference group.

*Reference group consists of patients with no or low-dose radiotherapy (eg, limb, head, neck or other minor field). RRs are adjusted for therapies with MOPP (1 variable), chlorambucil (1 variable), and other alkylating agents (1 variable).

†RRs are adjusted for cumulative dose of mechlorethamine (2 variables), duration of chlorambucil (2 variables), and therapy with other alkylating agents (1 variable).

‡Includes low to moderate irradiation doses to mantle/mediastinal fields (mean, 2980 cGy) or subdiaphragmatic fields (mean, 3140 cGy; eg, inverted Y, para-aortic, and pelvic).

§Includes high-dose irradiation to mantle/mediastinal fields (mean, 3900 cGy), or subdiaphragmatic fields (mean, 4200 cGy), or sub- or total lymphoid irradiation.

patients older than 45 years (RR = 4.9; 95% CI, 1.32-24.78, based on 13 cases/21 controls given TBI and 4 cases/30 controls who did not receive TBI); no association was found among those recipients younger than 45 years (RR = 0.9; 95% CI, 0.31-2.36; test of interaction, $P = .04$). Among patients who received TBI conditioning regimens after age 45 years, a larger proportion of cases than controls had low-grade NHL (62% versus 33%). Within this age group, similar intensity and duration of pretransplantation chemotherapy and radiation exposure were administered to cases and controls (data not shown). Data were too sparse to explore an age effect by TBI dose regimens.

Source of stem cells. Because the association with PBSC may partly reflect the clinical characteristics of patients selected to receive this type of graft, we separately evaluated leukemia risk among those who received PBSC because of poor bone marrow cellularity (and thus unsuitable for BM harvest). These patients (7 cases, 6 controls) had an increased risk of developing MDS/AML (RR = 4.3; 95% CI, 1.19-16.44; $P = .03$), compared with BM recipients in multivariate analyses. Risks for PBSC did not vary by primary disease in models adjusting for pretransplantation chemotherapy (data not shown). Data on number of reinfused cells for BM and PBSC grafts were incomplete and therefore not evaluated.

Other transplantation-related factors. Nonsignificant associations were found between MDS/AML and graft purging (RR = 1.6; 95% CI, 0.47-5.42; $P = .43$) or mobilization chemotherapy (RR = 1.7; 95% CI, 0.54-5.47; $P = .35$); no increase in risk was detected with use of etoposide for priming (RR = 0.7; 95% CI, 0.10-3.06; $P = .65$; 2 case patients, 9 controls).

Posttransplantation risk factors

About 34% of MDS/AML cases did not achieve complete remission or relapsed after transplantation, compared with 24% of controls (Table 1). Overall, there was a nonsignificant 1.7-fold risk

Table 4. Risk of myelodysplastic syndrome and acute myeloid leukemia according to pretransplantation therapy and transplantation-related factors

		Model 1: transplantation-related factors only			Model 2: transplantation-related factors, adjusting for pretransplantation chemotherapy		
Risk factors	Cases/controls	RR	95% CI	*P*	RR	95% CI	*P*
TBI dose, Gy*							
None	30/111	1.0	—	—	1.0	—	—
12.0 or less	18/52	1.5	0.68-3.32	.32	1.3	0.59-3.10	.48
13.2	8/5	6.6	1.90-27.11	.003	4.6	1.15-20.70	.03
				P_{trend} .008			P_{trend} .04
Source of stem cells							
Bone marrow	19/90	1.0	—	—	1.0	—	—
Peripheral blood ± bone marrow	37/78	2.3	1.20-4.53	.01	1.8	0.86-3.74	.12
Pretransplantation chemotherapy†							
Cyclophosphamide, no other AA	9/59				1.0	—	—
MOPP, mechlorethamine dose less than 50 mg/m^2	8/31				2.0	0.45-8.67	.36
MOPP, mechlorethamine dose 50 mg/m^2 or higher	12/24				4.3	0.97-19.69	.06
							P_{trend} .04
Chlorambucil, duration less than 10 months	4/5				3.8	0.68-20.09	.13
Chlorambucil, duration 10 months or longer	5/2				8.4	1.34-72.97	.02
							P_{trend} .009
Other AA, no MOPP, no chlorambucil	18/47				1.9	0.73-5.21	.20

RR indicates relative risk; CI, confidence interval; AA, alkylating agents; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; and —, reference group.

*Conditioning regimens with TBI given in the 12 participating transplant centers consisted of 4 dose protocols: 5, 10, 12, and 13.2 Gy. Risks of MDS/leukemia associated with TBI doses of 5.0 or 10.0, 12, and 13.2 Gy were 2.1 (95% CI, 0.51-7.24), 1.4 (95% CI, 0.58-3.19), and 6.5 (95%CI, 1.86-21.54), respectively (Model 1).

†Pretransplantation chemotherapy is included only in Model 2.

of MDS/AML in patients with persistent or recurrent disease after transplantation compared with those in complete remission (95% CI, 0.81-3.56; $P = .17$). Chemotherapy or radiotherapy given after transplantation did not appear to substantially modify MDS/AML risks in analyses of all lymphoma patients combined. However, in separate multivariate analyses for NHL and HD patients, risks associated with posttransplantation factors differed by primary disease. A significantly elevated leukemia risk was associated with persistent or recurrent disease (RR = 5.28; 95% CI, 1.46-25.28) among patients who underwent transplantation for HD, but not NHL patients (RR = 1.0; 95% CI, 0.37-2.75). MDS/AML cases were more likely to have received posttransplantation radiotherapy to treat relapsed or recurrent HD (37%) than controls (18%). There was no significant association with the use of posttransplantation growth factors (RR = 1.3; 95% CI, 0.58-2.83; $P = .57$).

Finally in univariate analyses, we observed 3- and 5-fold increased risks of MDS/AML among patients who failed to achieve platelet counts higher than 100×10^9/L ($P = .0008$) or granulocyte counts higher than 1.0×10^9/L ($P = .07$) after transplantation, respectively. Because these factors may be surrogate clinical markers of developing MDS/AML, we did not include them in multivariate analyses.

Discussion

This multi-institutional study is one of the largest investigations of secondary MDS/AML in autotransplant recipients. It is unique in providing extensive information on all pre- and posttransplantation therapies, including cumulative doses of selected leukemogenic drugs and estimates of radiation dose to bone marrow. Moreover, the participation of 12 transplantation centers allowed quantification of leukemia risk associated with various conditioning regimens and other transplantation-related factors. Our findings indicate that types and intensity of pretransplantation chemotherapy with alkylating agents are important risk factors of MDS/AML following autotransplantation for lymphoma. Transplantation-related factors such as conditioning regimens with TBI and source of stem cells may also influence the risk, although the weight of evidence for these findings is less strong.

Studies of lymphoma patients treated with conventional chemotherapy consistently report large increases in leukemia risk associated with alkylator-based therapies including mechlorethamine and chlorambucil.[19-22,39] Among patients with other cancers, high risks of secondary leukemia are reported for those treated with melphalan,[34,40] nitrosoureas,[41] cisplatin,[40,42] and high-dose etoposide.[43-46] As expected, our data demonstrate that pretransplantation therapies with MOPP, chlorambucil, and other high-risk alkylating agents are significant risk factors for MDS/AML developing after autotransplantation. These findings are further supported by the observation of significant dose-response relationships for mechlorethamine and chlorambucil. We found no evidence for an association between MDS/AML and pretransplantation etoposide, possibly explained by low average cumulative doses in our study. At least 5 investigations of transplant recipients have failed to detect an association between secondary MDS/AML and pretransplantation chemotherapy,[3,7,8,10,11] likely due to either incomplete pretransplantation data, inability to conduct separate analyses for high-risk drugs, or low statistical power. Other series have reported significantly increased risks with pretransplantation alkylating agents[6,9,18] and fludarabine.[13] The contribution of prior therapies in MDS/AML risk following autotransplantation is supported by laboratory studies showing pretransplantation clonal abnormalities predictive of subsequent MDS/AML, including loss of material from chromosomes 5 and 7 typically associated with exposure to alkylating agents.[47-49] The critical issue of pre-existing cytogenetic changes observed before transplantation could not be addressed in our study, as pretransplantation cytogenetic analyses were not routinely performed in several participating centers. Whether radiotherapy adds to already high risks associated with alkylating-based regimens remains uncertain in nontransplantation settings.[19,20,23,24] Significant associations between MDS/AML and prior radiotherapy are reported in some,[8,11] but not all[7,13] series of transplant recipients. No overall association was found in our data with pretransplantation radiotherapy, except possibly among the subgroup of patients with HD. Complete information on other leukemia risk factors (eg, smoking history, occupational or environmental factors) was not available in our study. It is unlikely, however, that such factors are associated with pretransplantation alkylating agents and high-dose TBI regimens, and would have a confounding effect.

Consensus on the possible leukemogenicity of conditioning regimens and harvesting procedures used for autotransplantation is lacking, in part because of a small numbers of cases[3,5,7,9,11,13,25] or use of uniform preparative regimens[6,8,9,13] in most transplantation studies. Although a large registry-based series is published,[10] this cohort study was limited by possible incomplete ascertainment of MDS/AML and only partial information on pretransplantation therapies. Some investigators report significant (or borderline significant) associations between risk of MDS/AML and conditioning with TBI,[3,10,25] PBSC graft,[5,7] VP16 for priming PBSC,[11] low count of infused cells,[8,11] and older age at transplantation.[3-5,10,25] Other series, however, show no excess risk with TBI[11] or PBSC.[10,11]

In contrast to most transplantation studies, we were able to analyze risk of MDS/AML associated with TBI dose. Overall, our investigation found no significant association with TBI, mostly used in NHL patients. Subgroup analyses, however, suggested that TBI dose 13.2 Gy was associated with an elevated risk, while there was no evidence of an increased risk of MDS/AML at TBI doses ranging from 5 to 12 Gy. The finding for high-dose TBI should be interpreted cautiously since this regimen was used at only one transplantation center that also implemented intensive follow-up after transplantation, including frequent bone marrow biopsies within the first year of transplantation. Several of the MDS/AML cases in this subgroup occurred shortly after transplantation, which provides additional evidence that leukemic cells may have existed prior to transplantation. In contrast, a previous study from Dana-Farber[8] reported a nonsignificant lower risk of MDS/AML for TBI at dose 14 Gy, compared with TBI 12 Gy or less, although follow-up for the high-dose TBI group was significantly shorter. The observation that host hematopoietic progenitor cells outlive the transplantation procedure raises the possibility that TBI conditioning may cause DNA damages to these surviving cells. Other mechanisms have been postulated to explain the potential leukemogenic effect of TBI, including modification of the microenvironment or alteration of immune surveillance.[50] Whether or not the impact of TBI on host cells is dose dependent remains unknown.

Some evidence in our data indicated that that increased risk of MDS/AML associated with TBI was limited to patients who underwent transplantation at older ages (> 45 years). This observation paralleled the findings from the University of Nebraska, a participant in the current study.[3] Moreover, the age difference in leukemia risk persisted after excluding this transplantation center

from our analyses. It is possible that the ability to repair DNA induced by TBI is most impaired among older patients.[51]

We estimated that risk of MDS/AML was approximately 80% higher in patients receiving PBSC graft than those with BM graft, although this result was not statistically different from no increase in risk ($P = .12$) after adjustment for the confounding effect of prior chemotherapy. Most importantly, PBSC grafts were not used routinely during the study period and a significant number of patients receiving these grafts did so because of poor cellularity of their marrow, a possible marker of preleukemic disturbed hematopoiesis. Our analyses support the fact that the association between MDS/AML and PBSC may reflect the clinical background of patients receiving this type of graft. Our finding that PBSC graft is not a strong independent risk factor of MDS/AML is consistent with the large series from the EBMT registry[10] and a recent study at the City of Hope[11] showing no association with PBSC grafts. Other investigators have reported approximately 4- to 6-fold increased risks of MDS/AML with PBSC grafts based on 10 or fewer MDS/AML case patients.[5,7] Priming with etoposide for PBSC collection has been linked to an elevated risk of MDS/AML.[11] Our data did not confirm this finding; few subjects, however, were given this treatment. Because growth factors are generally used to mobilize PBSC, it was not possible to evaluate their independent contribution to leukemia risk. Development of abnormal cells after engraftment with PBSC could be related to changes in the marrow milieu and immune function, as well as selection of aberrant progenitors by growth-factor therapy.[7,50]

A characteristic inherent to studies of secondary MDS/AML is the heterogeneity of conventional chemotherapy resulting in a large number of drugs to be evaluated. Correlations between prior treatment regimens and transplantation-related factors further limit the ability to fully adjust in multivariate models for these carcinogenic pretransplantation therapies. Because follow-up of transplant recipients in our base cohort was relatively short, risk patterns for long-term survivors may differ from those observed in our study.

Autotransplantation successfully increases survival of patients with relapsed or recurrent lymphoma.[14-17] We found in our study that type and intensity of pretransplantation chemotherapy contribute substantially to secondary MDS/AML in these transplant recipients. We cannot rule out, however, that transplantation-related factors also add to this risk. Our finding of an apparent association between MDS/AML and high-dose TBI (13.2 Gy), regimens that were infrequently used, needs to be confirmed. Our results reflect the experience of patients who underwent transplantation and were treated with earlier intense conventional therapies when mechlorethamine and chlorambucil were more widely used as first-line therapies for HD and NHL, respectively. Therefore, assessment of the risk-benefit of serial chemotherapy regimens should be evaluated with current treatment practices. Further investigations are needed to determine whether lymphoma patients unlikely to be cured with conventional therapy should be considered early for autotransplantation, in an attempt to control the disease while reducing the risk of secondary MDS/AML. Also, pretransplantation screening for abnormal karyotypes that are compatible with alkylator-induced MDS/AML should be performed to evaluate the hazards of autotransplantation or alternate allogeneic transplantation therapy.

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